REMARKS

STATUS OF THE CLAIMS

Claims 1-20 were pending in this application. Claims 15-20 have been cancelled without prejudice. Claims 1 and 11 have been amended. New claims 21-24 have been added. Following entry of the amendments, claims 1-14 and 21-24 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claims 1 and 11 have been amended to include the term "SEQ ID NO: 3" to more clearly define Applicant's invention as a compound targeted to a nucleic acid molecule of SEQ ID NO: 3 encoding Ship-1 (Claim 1) and a compound that specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule of SEQ ID NO: 3 encoding Ship-1 (Claim 11). Support for this amendment can be found throughout the specification as filed, e.g., page 79, lines 14-17, disclosing the human Ship-1 sequence using published sequence information (GenBank accession number U57650.1), which is incorporated as SEQ ID NO: 3, and page 80, line 35 through page 81, lines 1-5, along with Table 1 on pages 81-83, disclosing oligonucleotides designed to target human Ship-1, SEQ ID NO: 3.

Support for new claims 21 and 23 can be found at, e.g., Table 1 on pages 81-83 disclosing antisense oligonucleotides of 20 nucleobases in length, and on page 11, lines 32-36 and page 12, lines 1-2, disclosing oligonucleotides of 8 to about 50 nucleobases in length.

Support for new claims 22 and 24 can be found at, e.g., Table 1 on pages 81-83, disclosing various percentages of inhibition of human Ship-1 mRNA levels by chimeric phosphorothioate oligonucleotides, and page 81 disclosing antisense oligonucleotides comprising 40% inhibition of expression as one embodiment of the invention .

The amendments to the claims therefore add no new matter and entry is respectfully requested.

ELECTION/RESTRICTION REQUIREMENT

Pursuant to the restriction requirement made final and election of claims 2-10 and 12-14 (Group I), Applicant cancels claims 15-20 with entry of this amendment. Applicant reserves the

right to file subsequent applications claiming the canceled subject matter. In addition, the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. As described in the Office Action of March 12, 2004, the restriction of claim 3 (to which Applicant responded by electing SEQ ID NO: 21), is subject to the non-allowance of linking claim 1. Upon the allowance of linking claim 1, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the instant application.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-14 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner stated that the Applicants are "not considered to be in possession of the genus of any antisense molecule targeting any Ship-1 molecule," and the Examiner noted that the rejected claims "do not recite any sequence identifier." Additionally, the Examiner stated that the "specification discloses only antisense sequences targeted to a single Ship-1 sequence (SEQ ID NO: 3)," and further stated that this is "not considered to provide support for possession of the genus of any antisense molecules targeted to any Ship-1 molecule."

Without agreeing with the Examiner's rejection but to expedite prosecution of this application, Applicant has amended claims 1 and 11 to include a sequence identifier (SEQ ID NO: 3). Applicant requests withdrawal of this rejection as drawn to the amended claims.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 1, 2, 4, 5, 11, 12, and 14 were rejected under 35 U.S.C. 102(b) as allegedly being unpatentable over Rohrschneider *et al.* (WO 97/10252). The Examiner stated that "Rohrschneider teach antisense compounds at least 11 nucleobases long that target Ship-1, wherein said compounds target the active site of Ship-1, and comprise internucleoside modifications including phosphorothioate modifications, and compositions comprising said

compounds and pharmaceutically acceptable diluents thereof." Applicant respectfully disagrees with this rejection.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Rohrschneider fails to teach each and every element of the claimed invention. Nowhere does Rohrschneider disclose a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding Ship-1 (SEQ ID NO: 3), since Rohrschneider does not reference a nucleic acid molecule having the sequence of SEQ ID NO: 3 or any sequence at all that encodes Ship-1. Rohrschneider refers to human Ship-1 and provides a SEQ ID NO., while failing to provide the actual sequence of human Ship-1 in any sequence listing or otherwise within the reference. Rohrschneider further fails to disclose a compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding Ship-1 (SEQ ID NO: 3).

As addressed in the specification of the current application, Rohrschneider discloses at most "antisense inhibition of overexpressed or mutant Ship-1," but specific antisense sequences that are used in inhibiting expression are not provided (page 3, lines 11-14). Rohrschneider only discloses two antisense primer sequences, and these sequences are only referenced for use in PCR amplification to generate a radiolabeled probe. Nowhere does Rohrschneider disclose antisense sequences that are used to inhibit expression (nor possibly even suitable for inhibition of expression), and Rohrschneider does not provide any data regarding inhibition of expression by antisense oligonucleotides.

Thus, Rohrschneider does not anticipate the claimed invention and Applicant respectfully requests that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1, 2, and 4-14 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rohrschneider *et al.* (WO 97/10252), in view of Ware *et al.* (Blood 1996, 88:2833-40, AL), Taylor et al. (Drug Disc. Today, 1999. 4 (12)562-567) and Baracchini et al. (U. S. Patent Number 5,801,154). Applicant respectfully disagrees with this rejection.

Three requirements must be met for a prima facie case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the references or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The combination of art does not provide a motivation or teaching to combine the teachings to produce the claimed invention. The Examiner stated that one would have been motivated to create the "Ship-1 specific antisense sequences of Rohrschneider et al., and incorporate into them the specific length requirements and modifications as taught by Taylor et al. and Baracchini et al. for inhibition of Ship-1 expression ... because Rohrschneider et al. expressly teach phosphorothioate-modified antisense compounds directed to the Ship-1 target, and because Baracchini et al. teach the same antisense oligo modifications as instantly claimed, and indicate that modifications as taught by Rohrschneider and Baracchini provide for an antisense compound's increased cellular uptake, target affinity and resistance to degradation."

Applicant respectfully points out that the cited art does not teach or provide a motivation to combine the teachings to produce the claimed invention, but instead provides, at most, a generalized scientific goal, e.g., a goal to create and test antisense compounds targeted to any Ship-1 sequence with various lengths and modifications.

Rohrschneider provides a very generalized goal to prepare antisense oligonucleotides targeted to an unidentified Ship-1 sequence and discloses only two antisense primer sequences (for use in generating a probe) with unknown hybridization and/or inhibition activity. Rohrschneider provides no specific guidance on designing or selecting antisense oligonucleotides targeted to the specific Ship-1 sequence of SEQ ID NO: 3 for inhibition of expression. Beyond failing to provide specific explanation or examples regarding how to design antisense oligonucleotides targeted to Ship-1, Rohrschneider further fails to provide any guidance on how to make antisense compounds comprising phosphorothioate and other modifications.

Rohrschneider does not suggest making compositions comprising antisense compounds or pharmaceutically acceptable diluents thereof, nor does Rohrschneider explain how to make such compositions or diluents. As the Examiner admits, Rohrschneider also fails to teach antisense sequences comprising specific nucleobase and 2' modifications, or chimeras.

Baracchini fails to remedy these deficiencies. Barrachini does not provide a general teaching to designing antisense compounds to any target, but rather teaches designing antisense oligonucleotides to MRP and teaches the sequences of the specific antisense molecules targeted to MRP. There is nothing in Baracchini that is a generic teaching that could provide direction as to the successful selection of antisense molecules that would specifically hybridize with and inhibit expression of the Ship-1 (SEQ ID NO:3) nucleic acid molecule, given the completely unrelated sequences of Ship-1 and MRP.

Neither Taylor nor Ware provide a motivation to combine the references. Taylor provides a generalized review of antisense technology, but does not provide guidance as to *how* to design antisense oligonucleotides, much less how to design antisense oligonucleotides targeted to Ship-1 (SEQ ID NO:3). Ware provides guidance regarding cloning of human Ship-1 (SEQ ID NO:3), but does not provide any teaching regarding antisense technology directed to this target.

A generalized scientific goal cannot substitute for the particularity needed to establish a *prima facie* case of obviousness. The Examiner has not met the required specificity to establish a motivation to combine the references. The Examiner must show "reasons that the skilled artisans, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458, 1453 (Fed. Cir. 1998).

Therefore, the combination of references cited by the Examiner fails to make out a *prima facie* case of obviousness because "a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d at 1559, 34 USPQ2d at 1216.

The combination of cited references fails to provide a reasonable expectation of success. Assuming that the combination of art cited against the claims does contain all the claim

elements (and Applicant does not concede that it does), one of skill in the art would have had no expectation of success when combining the elements. Applicant notes that the combination of cited references fails to provide direction as to which of many possible choices of Ship-1 antisense molecules targeted to SEQ ID NO:3 is likely to be successful. As such, the cited combination at best makes the claimed invention "obvious to try." It does not render it obvious. See *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

The Examiner stated "... one would have a reasonable expectation of success given that ... Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and finally since Baracchini et al. teach making modified antisense compounds targeted to distinct regions of a target gene and methods of screening for successful gene inhibition, the steps of which are routine to one of ordinary skill in the art."

First, Applicant respectfully points that the cited passage from Taylor is not an example of Taylor providing an expectation of success. The complete quote from Taylor is a follows:

> The best target sites are still determined empirically, although improvements in the potency of ONs and in the algorithms used for predicting accessible sites on the target mRNA have drastically reduced the number of oligonucleotides that must be screened to fine one that is effective. Previous recommendations required the screening of 30-60 ONs per gene. Using high affinity chimeric oligomers and a bioinformatic program to select accessible sites, Woolf and coworkers have found that screening 3-6 oligomers per target is sufficient to find one that inhibits the gene with 66-95% efficiency (Sequitur, Natick, MA, USA) (unpublished data) ...

Clearly Taylor teaches that one of skill *cannot* predict specific active sequences without experimentation. One of skill in the art would conclude that Taylor does not teach how to design or select an oligonucleotide with antisense activity to any target (much less targeted to Ship-1 (SEQ ID NO:3), but rather Taylor discloses that Sequitur has designed and/or or selected *chimeric* oligonucleotides (with antisense activity) of unknown sequences targeted to an unknown target (e.g., not to *any* target), *using unpublished data, e.g., using methods that are not publicly known.*

Second, there is nothing in the approaches to designing antisense oligonucleotides used by Baracchini, nor in the sequences of the specific antisense molecules found by Baracchini that suggests that one of ordinary skill in the art would read the Baracchini disclosure regarding MRP as a generic teaching that could provide direction as to the successful selection of antisense molecules that would specifically hybridize with and inhibit expression of a Ship-1 (SEQ ID NO:3) nucleic acid molecule, given the completely unrelated sequences of Ship-1 and MRP. Accordingly, a *prima facie* case of obviousness has not been presented and withdrawal of this ground of rejection of the claims is respectfully requested.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (650) 335-7185.

Respectfully submitted,
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